REMARKS

Claims 1–12 and 14-31 are currently pending in the application. Claims 17–31 have been withdrawn previously. Claim 13 has been cancelled previously. Claims 1–12 and 14–16 are under consideration.

Claim 14 is cancelled. Claims 1, 15 and 16 are currently amended. No new claims are added. No new matter has been added, support for the amendments being found throughout the claims and specification.

Rejection Under 35 U.S.C. §112, First Paragraph

The Office Action argues that claims 12 and 14–16 stand rejected under 35 USC §112, first paragraph, because "the specification, while being enabling for a method of preparing an immunoglobulin expressing cell line capable of directed constitutive hypermutation of target sequence wherein the rate of mutation in the cell is modulated by administering a mutagen or homozygous deletion of XRCC2 or XRCC3, does not reasonably provide enablement for the method wherein the rate of mutation is modulated by expression of any sequence modifying gene product or any deletion, conversion or insertion (Office Action, p.3)." Applicants respectfully traverse the rejection.

The standard for determining whether the specification enables the claimed invention is whether it would permit one of skill in the art to practice the invention without the need to resort to undue experimentation. The Examiner argues that although the relative level of skill in the art is high, the skilled artisan would not be able to practice the full scope of the claimed invention without having to engage in undue experimentation.

Applicants respectfully disagree with the Examiner's position; however, solely in the interest of advancing prosecution and gaining allowance of the claims at issue, Applicants have amended the claims to recite that "the rate of mutation in the cell is modulated by genetic manipulation *of one or more DNA repair genes* (emphasis added)."

The term "DNA repair genes" is an art recognized term that includes a specifically defined set of genes, which were described and known to one of skill in the art at the time the present application was filed (see, for example Cui, X.et al. Mutat Res 434, 75-88. (1999); Griffin, C. S. et al. Nat Cell Biol 2, 757-761. (2000)). Since these genes, by definition, are

involved in DNA repair, it is consistent that modulating their activity or expression would influence, at least to some degree, the overall rate of mutation observed in a cell line capable of constitutive hypermutation. Further Applicants point out that the instant specification contains ample support to demonstrate that the rate of mutation in a cell can be modulated by genetic manipulation of one or more DNA repair genes. In the Examples, Applicants provide detailed experimental support to enable one of skill in the art to practice the invention as claimed. In particular, Applicants direct the Examiner to Example 8 of the specification, which teaches the selection of a constitutively hypermutating cell line.

The Examiner argues that the Sale et al. reference ((2001) *Nature*. 412: 921-926; cited in 11/14/2005 Office Action) teaches that the ablation of Rad51 paralogs increased somatic hypermutation while ablation of the closely related genes Rad 54 and Rad 52 had no effect on the hypermutation rate of the cell line studied. The Examiner argues that this teaching demonstrates the general unpredictability of modulating the rate of mutation in the cell by genetically modifying specific genes (Office Action, p.3).

Applicants direct the Examiner to Figure 19 of the instant application, which shows the effect of deletion of the various genes tested on the observed rate of surface Ig lost from each cell line, which is a measure of the rate of gene conversion in these cell lines. It is important to note that the wild type DT40 cell line exhibited a rate of constitutive mutation which is within the scope of the term "hypermutation", *i.e.* exhibited a rate of mutation which was greatly in excess of background mutation rates found in normal cells. See for example, paragraph [0013]:

> 'Hypermutation' refers to the mutation of a nucleic acid in a cell at a rate above background. Preferably, hypermutation refers to a rate of mutation of between 10-5 and 10-3 bp-1 generation-1."

Further, Applicants point out that paragraph [0196] of the specification describes the observed mutation rate in wild type and ΔXRCC2-DT40 cells:

> The mutation prevalences in these data sets are 1.6 x 10-3 mutations.bp -1 for VH, 0.03 X 10-3 for the unrearranged Vλ1 and 0.13 x 10 -3 for Cλ as compared to 2.0 X 10-3 for point mutations in the rearranged Vλ1 in the ΔXRCC2-

> DT40, 0.13 X 10-3 for point mutations in rearranged Vλ1 in wild type DT40 and 0.04 X 10 -3 for background PCR error.

Moreover, Figure 19, and associated data, teaches effects of genetic manipulations of these genes on the mutation rate, and in fact confirms the concept that these genes are capable of modulating (i.e. increasing, or decreasing) the rate of mutation. Specifically, Figure 19 B of the present specification illustrates that genetic manipulation of all four DNA repair genes tested results in a modulation of the rate of mutation in the DT40 cell type:

WT	0.47
ΔRAd54	0.05
ΔRAD52	0.36
ΔXRCC2	6.44
ΔXRCC3	2.31

Applicants point out that the claims at issue are not limited to "an increase" in mutation rate, but recite the term "modulate" which can equally refer to an increase or decrease in mutation rate. See, for example, paragraph [0094] – [0095] of the specification which teaches:

> Genes which are responsible for modulation of mutation rates include, in general, in nucleic acid repair procedures in the cell. Genes which are manipulated in accordance with the present invention may be upregulated, downregulated or deleted.
>
> Up- or down-regulation refers to an increase, or decrease, in activity of the gene product encoded by the gene in question by at least 10%, preferably 25%, more preferably 40, 50, 60, 70, 80, 90, 95, 99% or more. Upregulation may of course represent an increase in activity of over 100%, such as 200% or 500%. A gene which is 100% downregulated is functionally deleted and is referred to herein as "deleted".

The fact that deletion of four different DNA repair genes resulted in different effects on the overall rate of gene conversion is consistent with the idea that genetic manipulation of DNA repair genes will, as one might expect, modulate the observed mutation rate.

Accordingly, Applicants have established that the genetic modification of representative members of the genus of DNA repair enzymes do modulate the overall rate of mutation observed within a cell that exhibits constitutive hypermutation.

Thus, the currently amended claims are enabled by the specification and do not require undue experimentation in order to practice the claimed invention to the full scope because the claim requires only a "modulation" of mutation rate, and because DNA repair enzymes, and the recited methods of genetic manipulation, i.e. gene deletion, conversion, and insertion are well known to those of skill in the art.

The Examiner further argues that "Sale et al., demonstrates the general unpredictability of modulating the rate of mutation in a cell by deletion, conversion or insertion of specific genes. In view of this, one of ordinary skill would have no basis to distinguish those manipulations likely to be useful in the claimed method from those that would not be useful (Office Action, p. 3- 4)"

Applicants respectfully disagree. One can readily conceive of situations where both higher, or lower, rates of mutation provided by the claimed methods would be useful in specific methods and cell lines. An example is shown in the methods of claims 17-28 of the instant application, which include methods related to an iterative preparation of improved gene products comprising cycles of mutagenesis followed by selection.

Further, determining the degree of modulation of mutation rate would require no more than routine experimentation, *i.e.*, the genetic manipulation of the known DNA repair gene of interest, and testing the rate of mutagenesis, as taught in the present specification. Such methods amount to no more than routine experimentation, because of the extensive teaching of the present specification as described above, and because the level of skill in the art is high.

The courts have consistently ruled that such routine testing does not amount to undue experimentation. In *In re Wands*, the court stated that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. 'The key word is 'undue' not 'experimentation' (citing *In re Angstadt*, 537 F. 2d 498 at 504, 190 U.S.P.Q. 214 at 219 (C.C.P.A. 1976)). The Court also stated that "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction

in which the experimentation should proceed." (citing *In re Jackson*, 217 U.S.P.Q. 804 at 807 (Bd. App. 1982)). See also *Ex parte Foreman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

As such, the specification provides sufficient disclosure for one of skill in the art to practice the claimed method without resorting to undue experimentation. Applicants respectfully request withdrawal of the rejection and allowance of the claims.

Rejection Under 35 U.S.C. §102(b)

The Office Action argues that claims 1-12 are rejected under §102(b) as anticipated by Sale et al. (WO 00/22111, the '111 reference). The Office Action states that the '111 reference teaches each element of claim 1, with the exception of the requirement that the rate of mutation is modulated by genetic manipulation. The Office Action states that claim 10 of the '111 reference recites "that the rate of mutation in the cell is modulated by the administration of a mutagen which constitutes genetic manipulation of the cell." Applicants respectfully traverse the rejection.

Claim 1 has been amended to recite that the rate of mutation in the cell is modulated by genetic manipulation of one or more DNA repair genes. The '111 reference does not teach the genetic manipulation of a DNA repair gene to modulate the rate of mutagenesis. Accordingly, the '111 reference fails to teach every element of amended claim 1, and therefore does not anticipate amended claim 1. Each of claims 2 – 12 are directly or indirectly dependent from claim 1, and thus, incorporate all the features of claim 1, including that the rate of mutation in the cell is modulated by genetic manipulation of one or more DNA repair genes. Accordingly, the '111 reference does not anticipate any claim depending from claim 1.

Applicants respectfully request that the rejection be withdrawn and allowance of the claims.

Double Patenting

The Office Action states that "claims 1 – 12 stand rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 1, 36, 37, 39, and 40 of co-pending application 10/146,505 (now US Patent No. 7,122,339) in view of Montiero et al. (2000) (Office Action, p.5).".

Upon notification of allowable subject matter in the instant case, Applicants will timely file a terminal disclaimer effective to obviate the double patenting rejection.

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

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